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Atropine Sulphate in General and GMP Regulation

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ABSTRACT: Atropine is an alkaloid with the chemical formula $C_{17}H_{23}NO_3$. It belongs to the tropane group of alkaloids, with tropane being a nitrogenous bicyclic organic compound with chemical formula $C_8H_{15}N$. Tropine is mainly known for a group of alkaloids derived from it (called tropane alkaloids).
The regulations set contain good manufacturing practice for methods to be used in the facilities or controls to be used for, the manufacture, processing, packing, holding of a drug to assure that such drug meets the requirements of the act as to safety and has identity, strength and meets the quality and purity characteristics that it purports or is represented to possess. What manufacturers need today is a more efficient handling of products and utilization of assets with compliance maintained. At the same time, the requirements from the FDA as well as other authorities are increasing, in particular regarding automated lines and the handling of electronic production data. Optimizing your manufacturing processes and shortening your lead-times is our mission. Our focus spans incoming to outgoing goods, from simple to highly automated lines, always with GMP regulations compliance at heart. Most importantly, we work in partnership with our customers in pursuit of efficiency and cost-effectiveness.
KEYWORDS: Atropine Sulphate eye ointment, GMP Regulation, Advancement & Future outlook of atropine ointment.

INTRODUCTION

OPHTHALMIC PRODUCTS[1]

These are the products which are to be instilled into the eye in the space between the eye lids & eye balls.
Ophthalmic preparation must be sterile and are prepared under the same condition and method as other parenteral preparations. They should be supplied on the single use container and any solution remaining at the end of the operation must be discarded.

PURPOSE OF OPHTHALMIC PREPARATION[1]

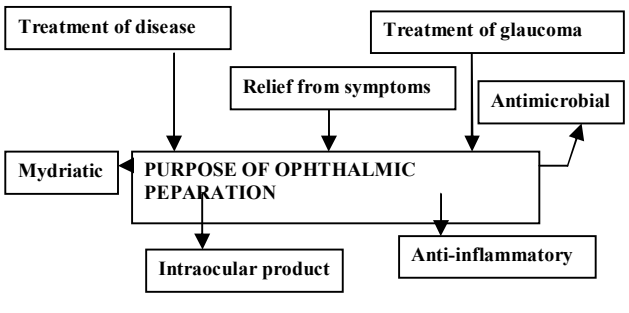


Fig: 1 Various purposes of Ophthalmic preparation

CLASSIFICATION OF OPHTHALMIC PRODUCTS[2]

Table-1 Some formulation of ophthalmic product

PREPARATION	EXAMPLES
1. LIQUIDS	Eye Drops, Eye Lotion
2. SEMI SOLIDS	Eye Ointment, Creams, Gels
3. INJECTIONS	Antisecretory (Atropine)

ATROPINE SULPHATE EYE OINTMENT: AT A GLANCE[2]

- Atropine is obtained from Atropa belladonna & is d, l-hyoscamine.
- L-isomer is more potent.
- Category- anticholinergic agent (Parasympathetic antagonist).

ATROPINE SULPHATE EYE OINTMENT [3]

Atropine sulphate ophthalmic ointment is atropine sulphate in a suitable ophthalmic ointment base, it contain not less than 90% & not more than 110% of the labeled amount of $(C_{17}H_{23}NO_3)_2$. H_2SO_4 .H_2O.

MODE OF ACTION

Atropine blocks the receptors in the muscles of the eye (muscarinic receptors). These receptors are involved in controlling the pupil size and the shape of the lens. By blocking these receptors, atropine produces dilatation of the pupil (mydriasis).

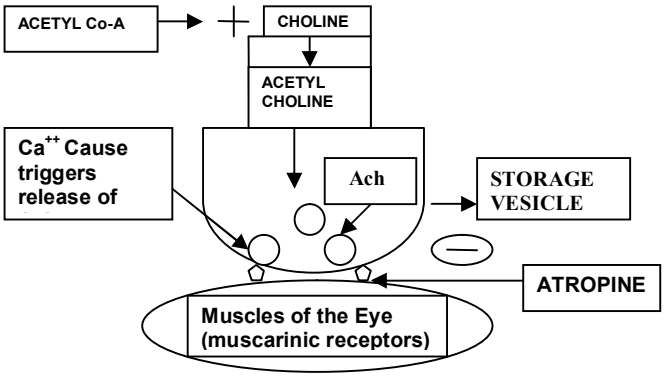


Fig: 2: Schematic presentation of mode of action of atropine in to eye

STORAGE [4]

A. Store at room temperature between 59 and 86 ºF (15 - 30 ºC) away from moisture and sunlight.
B. Do not freeze Atropine Sulfate.
C. Store solution in a cool and dark place.
D. Discard the solution if it turns brown, cloudy or contains particles.
E. Do not save for later use.

APPLICATION OF OINTMENT IN TO EYE[4]

a) To apply eye ointment, first wash your hands.
b) Be careful not to touch the dropper or let it touch your eye or any other surface.
c) Tilt your head back, gaze upward and pull down the lower eyelid to make a pouch.
d) Fill up eye with ointment & rub as gentle message with hand.
e) Look downward and gently close your eye for 1 or 2 minutes.
f) Apply gentle pressure to the corner of the eye to keep the medicine in and to minimize the possibility of Atropine Sulfate being absorbed by your body.

EFFECT AND PRECAUTION OF ATROPINE SULPHATE OINTMENT[4]

1. **SIDE EFFECT**
   - Dryness of mouth
   - Temporary drowsiness or blurred vision
   - Rash, Itching, Swelling, Dizziness
2. **ADVERSE EFFECT**
   - Hallucinations
   - An Irregular or Fast Heart Rate
   - Swelling Of Your Lips, Tongue, Face
3. **PRECAUTIONS**
   - Not use in glaucoma (narrow angle), Down's syndrome, allergies
   - Do not wear soft contact lenses while using Atropine Sulfate because the lenses may discolor.
   - Use caution when using Atropine Sulfate in children

USES[4]

- Dilating the pupil to aid examination of the eye
- Inflammation of the coloured part of the eye and the muscle
- It is also used for certain eye exams.

SHELF LIFE

The shelf-life is 24 months from the date of manufacturing.

CHEMICAL PROPERTIES OF ATROPINE SULPHATE AS EYE OINTMENT

Table 2: Chemical Properties of Atropine Sulphate as Eye Ointment[5]

PROPERTIES	SPECIFICATION
Name	Atropine sulphate
IUPAC name	Benzeneacetic acid, alpha- (hydroxymethyl)-8-methyl-8-azabicyclo{3.2.1}oct-3-yl ester, sulfate
Empirical formula	$(C_{17}H_{23}NO_3)_2.H_2SO_4.H_2O$
Molecular Mass	694.82
Melting point	190 to 194 ^oC
Physical state	Odourless, very bitter, Colorless crystals or White crystalline powder
Solubility	• One gram dissolves in 0.4 ml water. • One gram dissolves in 5 ml cold alcohol and 2.5 ml boiling alcohol, in 2.5 ml glycerol, 420 ml chloroform and 3,000 ml ether.
Optical properties	Inactive Optically
pK_a	9.8
P^H	A 2% solution in water has a pH of 4.5 to 6.2

GMP REGULATION OF ATROPINE SULPHATE EYE OINTMENT

GENERAL PROVISION FINISHED PRODUCT

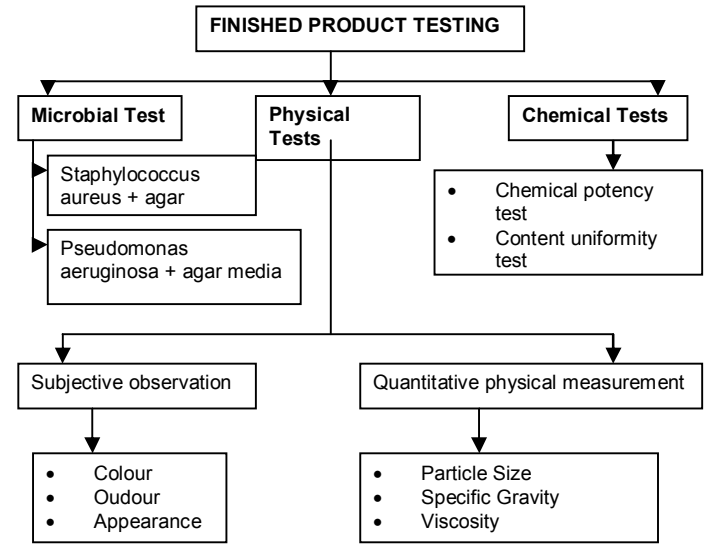


Fig 3: General outline of quality control of eye ointment

PERSONNEL[6]

1. All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work.

2. Personnel should be given relevant information and training in hygiene and microbiology.
3. Personnel should have proper knowledge of ointment manufacturing in sterile area.
4. Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology and veterinary medicine.
5. The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated.

BUILDINGS[6]

Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production process (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area. Control panel visually shows all operations of the plant on a mimic display. Continuously variable speed control of the mixing arm is achieved by AC frequency controller. Digital display of product temperature and current values on the control panel

1. The building shall be built on proper foundation with standard materials to avoid cracks in critical areas like aseptic solution preparations are needed.
2. Location of services like water, steam, gases etc. shall be such that there is no problem in production.
3. In aseptic areas

a. Walls, floor and ceiling should be clear, non-shedding & non-cracking.
b. Walls shall be flat & ledges and recesses shall be avoided. Wherever other surface joint in the wall and the floor should be avoided.
c. There are no sinks & drains.
d. The furniture should be smooth & washable.

EQUIPMENTS[3, 7]

- Cold Rooms.
- Autoclaves
- Clean room facility at Class 10,000 level.
- Laminar Blister forming machineries
- Flow Benches at Class 100 level.
- Refrigerator

LIQUID FILLER EQUIPMENT

- Capacities ------- range from 15ml up to 1 gallon neck finishes of 28 mm and larger.
- Facilitated by warming the product to reduce the viscosity.
- Careful to avoid: chemical degradation, sedimentation of suspended solid if excessive reduction in viscosity by heating.

For viscous product that contain surfactants, prone to aeration

- accelerate oxidation
- produce bubbles
- interfere with pumping - right amount of product not delivered to the container)

RAW MATERIAL[8]

Table 3: Required raw materials

Raw Materials	Parameter
1. Ointment Base	Yellow Soft Paraffin, Liquid Paraffin, Hard Paraffin, Lanolin
2. Drug	Atropine sulphate
3. Antimicrobial agent	Benzalkonium Chloride (0.01% $^{w}/_{v}$), Benzyl alcohol (1-2% $^{w}/_{v}$), Phenylmercuric salts (0.002% $^{w}/_{v}$)
4. Antioxidant Agent	Bisulphites, Butylated hydroxy anisole.
5. Emulsifier	**Anionic--** Alkyl sulfates, **Cationic--** Quaternary ammonium, **Nonionic**-- Polyoxyethylene fatty acid
6. Gelling Agents	Tragacanth, Sodium Alginate
7. Permeation Enhancer	Menthol, Carvacrol, Geraniol, Nerolidol,Lecithin
8.Humectants	Poly Ethylene Glycol, Glycerol or Sorbitol
9.Fragrances	Lavender oil, Rose oil, Lemon oil, Almond oil

PRODUCTION & CONTROL OF ATROPINE EYE OINTMENT

a) GENERAL STEPS OF MANUFACTURING PROCESS OF OINTMENT[9]

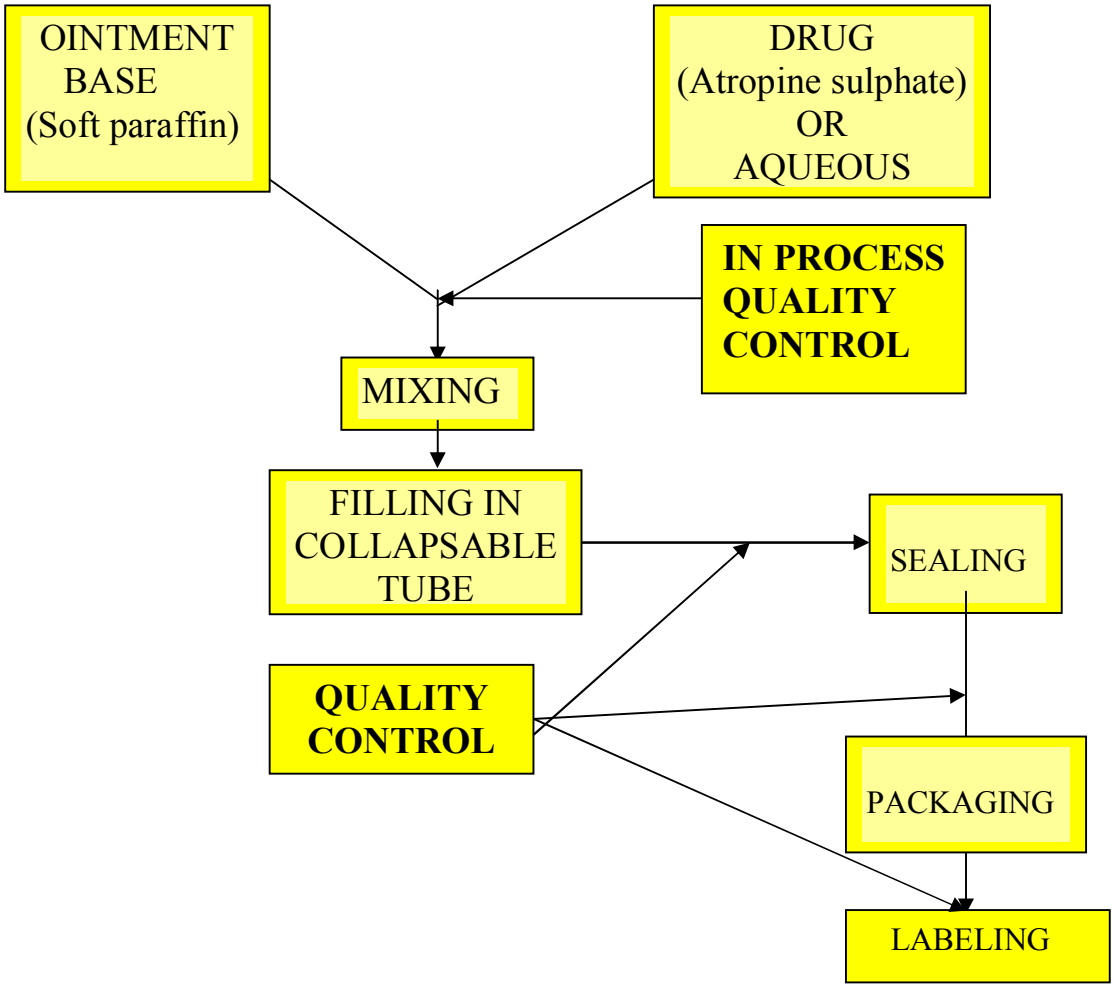


Fig 4: Schematic representation of manufacturing process of eye ointment

b) IN PROCESS QUALITY CONTROL[10]

Sterile formulations must meet a number of special criteria such as:

a. Sterility
- Membrane filtration
- Direct inoculum

b. Particulate material
- 0.5-5 micron Particles in clean area room

c. Pyrogen free
- LAL test(Limulus Amoebocyte Lysate)

d. Stability
- At 40 ± 2˚C / 70 ± 5 % RH

e. pH
- 6.2-6.8 (Isotonic to eyes)

f. Osmotic pressure

g. Uniformity of distribution of active ingredients

h. Viscosity measurement
- Capillary method, Ostwald viscometer

c) STANDERDISATION[11]

1. We performed a comparative analysis of several batches of the new ointment immediately after preparation and upon holding under "accelerated aging" conditions (at 40 °C) for a time equivalent to 3-year storage under normal conditions. The ointment appears as an odorless homogeneous.
2. The quantitative analysis was performed by UV spectrophotometry. An exactly weighed

amount (~3 g) of the preparation was mixed with 10 ml of water in a 50 ml cone-shaped measuring flask with ground stopper and the content was vigorously agitated. To this mixture was added 10 ml of chloroform and stirring was continued for 10 min. Then the mixture was transferred to a separatory funnel and the bottom (chloroform) layer was discharged. The aqueous layer was transferred to a 50 ml measuring flask and the flask was filled with water to the mark (solution A). A 1-ml aliquot of solution A was placed into a 100-ml measuring flask and diluted with water to the mark (solution B). The optical density of solution B was measured in a 10 mm thick cell on a spectrophotometer tuned to the absorption maximum at 252 nm.

d) QUALITY CONTROL

1. Assay (I.P., 1996)[12]

1 g of atropine sulphate, accurately weighed, is dissolved in 50 ml of glacial acetic acid, then titrated with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. A blank determination is performed and any necessary corrections made. Each ml of 0.1 N perchloric acid should be equivalent to 67.68 mg of $(C_{17}H_{23}NO_3)_2$. H_2SO_4.

2. Assay (BP, 2000)[13]

0.500 g of atropine sulphate is dissolved in 30 ml of anhydrous acetic acid R, warming if necessary. The solution is cooled then titrated with 0.1M perchloric acid and the end-point determined potentiometrically.1 ml of 0.1M perchloric acid should be equivalent to 67.68 mg of $C_{34}H_{48}N_2O_{10}S$.

PACKAGING & LABELING OF ATROPINE SULPHATE EYE OINTMENT[14]

Packaging Materials

Fabricated from:

- Metals
- Plastics, rubber
- Glass
- Any combination from the above

Containers for eye ointments

- Screw-capped amber glass
- Plastic pots but Methyl salicylate incompatible with plastic containers
- Collapsible metal tubes
- Tend to shed metal particles near their screw-threads

Ideal Closures

1. Seal the container to prevent loss of product
2. Withstand sterilization process
3. Prevent contamination by micro-organism
4. Non-reactive
5. Easily remove and replace the closure and reseal (best reseal with glass fusion)

Table 4: List of Packaging materials of ophthalmic ointment

Metals	Polymers – plastics
Tin Metal resistant Tin-coated tubes Eye ointment tubes **Iron** Fabrication of drums, screw caps **Aluminum** Low atomic weight, very reactive.	1. High MW with good thermal and electrical insulators 2. Less rigid, but can be as strong as metals. 3. High degree of resistance to inorganic reagents but softened or dissolved by organic solvents. E.g. PTFE, PP, PC, PE

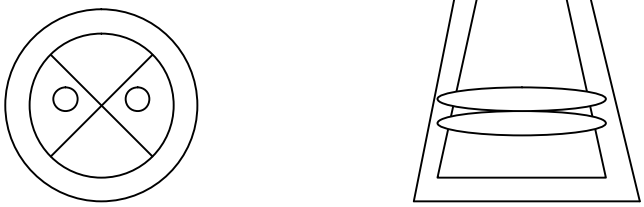
Types of closures

Some examples

I. Push-on
   - Bung
   - Oldest known closures

II. Screw-cap

III. Fusion – hermetic seal



(a)Bung (b) Screw-cap

Fig 5: Closures type

Labeling Of Atropine Sulphate Eye Ointment[15]

Table-5 Labels Include On Ophthalmic Preparations

Sr.No	Parameters	Instructions on label
1	State route of administration	For external use only
2	Fully identify the product	The name and concentration of active ingredients
3	Statement on preservation	Confirm presence or absence of preservative
4	Direction for use	Ex: Add one drop to each eye morning and evening.
5	Statement on in use expiry date	Day, month, year
6	Storage requirements	'Store in cool place' or 'Protect from light'
7	Identify patient	Patient's name
8	Date of dispensing	Day, month, year

Format of label of atropine eye ointment

THE OINTMENT
100g For: Mr. xx xxx Age: 18 years (F) Regd No: 184 FOR EXTERNAL USE ONLY Date of dispensing: 10/9/99 Direction: To be applied in the affected part two or Three times a day. Dispensed by:

DOCUMENTATION[16, 20]

The manufacturing records of atropine sulphate ointment indicate the following details:-

Table 6: Documentation of atropine sulphate eye ointment

Sr. no	Test
A.	**Raw material name**
1.	Structural formula, molecular weight
2.	Chemical name
3.	Item number
4.	Date of issue
5.	Date of superseded, if any, or new material
6.	Signature of writer
7	Signature of approval
B.	**Samples**
1.	Safety requirement
2.	Sample plan and procedure
3.	Sample size and sample container to be use
4.	Preservation sample requirement
C.	**Retest program**
1.	Retesting schedule
2.	Reanalysis to be perform to assure identity, strength, quality and purity
D.	**Specifications wherever applicable**
1.	Description
2.	Solubility
3.	Identity
a.	Specific chemical test
b.	Infrared absorption
c.	Ultraviolet absorption
d.	Melting range
e.	Congealing point
f.	Boiling point or range
g.	Thin layer, paper, liquid or gas chromatography
4.	Purity and quality
a.	General completeness of solutions, pH, specific rotation, non-volatile residue, ash, acid-insoluble ash, residue on ignition, loss on drying, water content, heavy metals, arsenic, lead, mercury, selenium, sulphate, chloride, carbonates, acid value , iodine value, saponification value
b.	Specific quality tests ,particle size, crystallinity characteristics ,and polymorphic forms
c.	Specific purity tests , related degenerated products
5.	Assay , calculated either on anhydrous or hydrous basis
6.	Microbial limit test, especially for raw materials from natural sources
E.	**Test procedure**

1.	Compendial USP or NF references
2.	Noncompendial, detailed analytical procedures, weights, dilutions, extraction
F.	**Approved suppliers**

PROTOCOL[17, 19]

MATERIAL SAFETY DATA SHEET

Issued: 09/07/94
Revised: 01/25/02
Revision: 01

Prepared by: Gary Wong
Manager EHS
Core No. 051

1. PRODUCT AND COMPANY IDENTIFICATION

Product Name: Atropine Sulfate Ophthalmic Ointment USP, 1%
Generic Name: Same
NDC No. 24208-825-55 (3.5 gm)

Legal Category: Prescription only medicine, filled inside plastic bottle suitable for dispensing, and overpacked inside a cardboard carton.

Drug Composition: Mydriatic (Opens pupil)

BAUSCH & LOMB PHARMACEUTICALS, INC.
8500 Hidden River Parkway
Tampa, FL 33637
Information: (800) 323-0000 (M-F) 8am-5pm EST
Emergency: (800) 227-1427 24 hrs

2. COMPOSITION/INFORMATION ON INGREDIENTS

Description	CAS #	TLV (mg/m^3)	PEL(mg/m^3)	% Content
Atropine Sulfate	55-48-1	NE	NE	≥1
Lanolin, Anhydrous	8006-54-0	NE	NE	≥1
Mineral Oil	8042-47-5	5(mist)	5	≥1
White Petrolatum	8009-03-8	NE	NE	≥1
Purified Water	7732-18-5	NE	NE	≥1

VALIDATION OF ATROPINE OINMTMENT[18]

- Written documentation
- Manufacturing parameter
- Testing parameter
- In process control
- Final product testing

ADVANCEMENT & FUTURE OUTLOOK OF ATROPIN EYE ONTMENT

Novel eye ointments are non greasy since they are made up of water washable bases. Hence they cause less irritation to skin and are superior to conventional semisolid dosage form.

Advancement by Need for combination therapy

e.g., cromoglycate and corticosteroid for asthma and allergies

The need for a predetermined profile of drug delivery over a prolonged period of days, weeks, or months e.g., acute corneal infections, acute-becoming chronic inflammation, and corneal graft rejection episodes

Long-continued low dosage for therapy or prophylaxis. e.g., for prevention of corneal graft rejection, prevention of recrudescence of inflammation and prevention of recurrence of hepatic disease.[6]

Ocular indication of controlled-release systems

a) Short, topical ocular half-life. **e.g.** heparin for ligneous disease
b) Small, topical ocular, therapeutic index. **e.g**. pilocarpine for chronic open-angle glaucoma , possibly nucleside, antiviral
c) Systemic side effects. **e.g.** timolol for glaucoma and cyclosporin A for graft rejection

The technologies described here represent small fraction of the development of drug delivery systems and few of them are still at experiment level. The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current systems can be improved if their delivery rate, biodegradation, and site-specific targeting can be predicted, monitored, and controlled. Which the help of rapid advances in biotechnology, chemistry, and chemical engineering, it will be possible for researchers to obtain drug delivery systems with minimum side effects and maximum effectiveness.[20]

CONLUSION

Atropine Sulfate Ophthalmic Ointment is Atropine Sulfate in a suitable ophthalmic ointment base. It contains not less than 90.0percent and not more than 110.0 percent of the labeled amount of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$.It is sterile. Atropine ophthalmic causes the muscles in your eye to become relaxed. This widens your pupil. Your pupil will remain wide and will not respond to light. Atropine ophthalmic is used to dilate (widen) your pupil when you have an inflammatory condition or in post surgery situations in which this effect may be helpful.

Atropine ophthalmic passes into breast milk in small quantities. Its effects on a nursing baby are unknown. Do not use atropine ophthalmic without first talking to your doctor if you are breast-feeding a baby. If you are over 65 years of age, there is a greater chance that you have increased pressure in your eyes.

Novel eye oiniments are non greasy since they are made up of water washable bases. Hence they cause less irritation to skin and are superior to conventional semisolid dosage form.

Novel eye ointments now days are provided with nanoparticles and microspheres, which has an excellent emollient effect, with better spreadability, and less staining than oleaginous ointments. However both medicated and non-medicated creams provide very good emollient effects, oleaginous ointments are preferred for dry, chapped skin in an environment of low humidity because of its occlusive properties.

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